

**Response under 37 C.F.R. 1.116
- Expedited Examining Procedure -
Examining Group 1723**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Rajesh V. Mehta, et al

Group Art Unit: 1723
Examiner: Joseph W. Drodge

**PROCESS FOR THE FORMATION
OF PARTICULATE MATERIAL**

Serial No. US 10/814,354
Filed 31 March 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

Sir:

Pre-Appeal Brief Request for Review

Applicants request review of the final rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a Notice of Appeal. The review is requested based on the following Arguments.

Arguments

The Examiner states that Saim et al ("Saim") disclose formation of micro or nano-particles by a process of admitting a supercritical fluid to a vessel, in which temperature and pressure are controlled (column 14, lines 21-45), agitating such vessel with a rotary agitator comprising an impeller of un-specified, given diameter relative to vessel diameter (column 14, line 63 column 15, line 6), introducing a 1st feed stream comprising a solvent and desired, active substance through a 1st introduction port and introducing a 2nd feed stream comprising the supercritical fluid through introduction ports both approximately within the highly agitated zone of the mixer that may be an impeller (see especially figures 1 and 2 and column 18, lines 30-63). The Examiner further states that both a first feed stream including particle-forming components and solvent and a second feed stream containing supercritical fluid may be introduced proximate the agitated/highly agitated zone of the mixer (see column 12, lines 11-12 taken with lines 33-36 of column 12), and that particles are then precipitated within such vessel over a carrier bed.

The Examiner further states that O'Connor et al ("O'Connor") teaches to produce nanoparticles using solvents and supercritical fluids by use of conversion/mixing vessels that combine impeller mixers with other type stirrers, that have inlets for introducing solvents and other materials, and/or have a plurality of impeller mixers or impellers with differently functioning blades so as to create different mixing zones of different degrees of turbulence, and that it would have been obvious to one of ordinary skill in the art to have adapted the more-complex configuration of mixing/agitating means of O'Connor in the process of Saim, to effect greater, more complete mixing of components which are in slurry form, or mixing of materials of different phases (liquids, solids, semi-solids and gases). The Examiner further states Johnson et al ("Johnson") teach production of nanoparticles using supercritical fluid processing in which the inlet tubes are within 15% of the agitator surface diameter (see especially paragraph 44, paragraphs 39-42, 58 and 63), and that it would have been obvious to one of ordinary skill in the art to have located the end of the inlet tubes of Saim very close to the impeller agitators as suggested by Johnson, to facilitate rapid incorporation of the incoming fluid into the swept region of the agitator and rapid mixing.

This rejection represents clear error, as the Examiner has misinterpreted the individual teachings of the cited references, and has further failed to establish a prima facie case of obviousness with regard to combining the teachings of such references so as to arrive at the present claimed invention, as each of such references employ distinct types or materials and or apparatuses for distinct purposes, and as the proposed combinations and modifications of the individual references go against the expressed preferences of the individual references.

Saim, e.g., is directed towards trapping (e.g., coating or dispersing) of precipitated particles in a bed of powder carrier material. While Saim teaches that the bed may be agitated to uniformly distribute precipitated solute particles throughout the mixed powder bed (col. 10, lines 59-67), such mixing is not even required, and such trapping or coating is not necessarily a rapid kinetic process as compared to the micromixing time scales associated with the precipitation of particles themselves. While a rotary agitator is disclosed for agitation of the bed of carrier material, Saim does not teach that both the first feed stream including particle-forming components and solvent and the second feed stream containing supercritical fluid should be introduced proximate an agitated/highly agitated zone of the mixer for the purpose of

formation of discrete particles having a size of less than 20 nm. In such connection, the Examiner's reliance upon column 12, lines 11-12 taken with lines 33-36 of column 12 is clearly in error, as lines 11-12 are directed towards a first "Mode 1" employing RESS techniques (and thus there are not separate first and second streams introduced into the vessel, but rather only a single pressurized stream which is expanded upon entry into the vessel), while lines 33-36, which are directed towards a SAS type process more similar to the present process, do not teach entry of the separate solutions and pressurized gaseous fluid in a highly agitated zone within one impeller diameter of the agitator impeller surface. Similarly, the Examiner's further reference in the Final Rejection to column 12, lines 8-36, column 13, lines 14-30, and column 15, lines 15-22 of Saim with respect to introduction of feed streams also does not teach such required feature of the claimed invention. To the contrary, Saim discloses in such cited sections a preference for the introduction of the pressurized gaseous fluid only from above an upper surface of the bed of carrier particles (i.e., clearly away from any highly turbulent zone that may be created by the mixer), and of the organic liquid solution from a level below or slightly above the upper surface of the bed of carrier particles, and mixing of the bed of carrier particles to coat the carrier particles with particles of material precipitated from the solution.

Accordingly, whether the impeller depicted in Fig 2 of Saim inherently creates two mixing zones or not as argued by the Examiner, there is simply no teaching or suggestion to introduce both feed streams into any created highly agitated zone created within one impeller diameter of the impeller surface so as to enable formation of discrete particles having a size of less than 20 nm, especially in view of the explicitly stated preferences for other introduction point locations taught by Saim discussed above. As Saim is clearly directed toward obtaining a specific result different from that of O'Connor and Johnson (i.e., coating of particles in a fluidized particulate bed), it clearly would not be "obvious" to change such process away from the specifically described preferences based on references which are not directed towards achieving such result.

It is further noted that the O'Connor process, although employing impellers and supercritical fluids, is directed towards the size reduction of pre-made macro particles, rather than the direct precipitation of small sized particles as is Saim. The physics of size reduction is fundamentally different from that of particle formation via precipitation, and accordingly no reasonable extrapolation can be made from the

proposed combination of the Saim process with the teachings of O'Connor. The Examiner has provided no reasonable explanation as to why one skilled in the art would combine the particle reduction process of O'Connor with the particle precipitation process of Saim, especially to the extent such combined teachings would be inconsistent with the expressly taught preferences of the process of Saim.

Regarding Johnson, the referenced teaching in paragraph [0044] thereof of employing inlet tubes which are within 15% of an agitator surface diameter is essentially duplicative of the already acknowledged prior art mixing technology discussed at page 9, lines 24-31 and the paragraph bridging pages 10-11 of the specification. What is not taught or suggested, by either Johnson or the acknowledged prior art mixing technology, is to employ such type known type of mixing technology apparatus in a SAS type particle formation process. To the contrary, Johnson is directed towards making of nanoparticles of amphiphilic copolymers in conventional liquid solvents. In such connection, referenced paragraph [0058] of Johnson is not directed towards a teaching of supercritical fluid introduction during the process of nanoparticle formation as alleged by the Examiner, but rather discloses the use of liquefied gas (not a supercritical fluid) as a non-process solvent, while referenced paragraph [0063] states that the final solvent containing the formed amphiphilic copolymer nanoparticles can be subsequently altered by a supercritical fluid extraction post treatment process. Accordingly, there is no support for the Examiner's assertion that Johnson teach production of nanoparticles using supercritical fluid processing, and the process of Johnson does not enable production of particles having a volume-weighted average diameter of below 20 nm as required by claim 1.

It is further noted that Johnson actually teaches that an agitator is not even required in the disclosed process if the fluids added into a non-solvent have a high mixing velocity sufficient to mix the fluid contents rapidly and in a controlled fashion (see, e.g., last 4 lines of paragraph [0017]). Supercritical fluids as required in the present invention are known to have gas-like transport properties, as noted at page 1, line 10 of the specification. For micromixing, the critical transport property of interest is molecular diffusivity. Gas-like molecular diffusivity lowers mixing time to levels not attainable in liquids. Thus, Johnson's teaching that an agitator is not need where the fluids are combined in a manner otherwise providing a high mixing velocity (such as may be provided by the high molecular diffusivity provided by the

gas-like transport properties of super-critical fluids) in fact would appear to teach that a mixer would not be required for mixing in supercritical fluids, thus teaching away from the present invention, which is consistent with the preferences taught in Saim of adding the supercritical fluid above the mixed bed.

Finally, while it is believed that a prima facie case of obviousness has not been established based on the arguments above, it is further noted that any such alleged prima facie case of obvious is in any event overcome by the surprising results of the present invention. As disclosed in Examples 4-8 of the present application, the invention enables production of particles less than 20 nm in diameter for a number of materials, many of them substantially smaller than even 10 nm, while none of the cited references teach a process which enables such small particle size. The Examiner's reference to column 9, lines 39-42 of Saim as a teaching of obtaining particles having diameters as small as 0.001 micron (1 nanometer) may be formed does not equate to an enablement of such particle size. Rather, Saim only uses such 0.001 micron as a lower limit for a definition of "nanoparticles". Saim has not demonstrated formation of discrete nanoparticles in the size range of less than 20 nm, and to the contrary, the designation therein at col. 9 lines 39-42 of nanoparticles "preferably" having an average particle diameter in the range of about 0.05 to 0.5 micron (i.e., 50 to 500 nm) is evidence of the non-obviousness of the present invention's ability to achieve particles have an average size of less than 20 nm. Reversal of this rejection is accordingly respectfully requested.

The final rejection being clearly in error for at least the reasons asserted above, a prompt and favorable action in response to this request is earnestly solicited.

Respectfully submitted,



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If the Examiner is unable to reach the Applicant(s) Attorney at the telephone number provided, the Examiner is requested to communicate with Eastman Kodak Company Patent Operations at (585) 477-4656.